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(54) Title: THE USE OF SOLUBLE FLUOROSURFACTANTS FOR THE PREPARATION OF METERED-DOSE AEROSOL FORMULATIONS

(57) Abstract

Pharmaceutical suspension aerosol formulations using one or more perfluorinated sulfonamido alcohol phosphate esters as surface-active dispersing agents and 1,1,1,2-tetra-fluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, or a mixture thereof, as the propellant.

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THE USE OF SOLUBLE FLUOROSURFACTANTS FOR THE PREPARATION OF METERED-DOSE AEROSOL FORMULATIONS

TECHNICAL FIELD OF THE INVENTION

This invention relates to suspension aerosol formulations suitable for the administration of medicaments. More particularly, it relates to pharmaceutical suspension aerosol formulations using 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane as the propellant.

BACKGROUND OF THE INVENTION

Pharmaceutical suspension aerosol formulations currently use a mixture of liquid chlorofluorocarbons as the propellant. Fluorotrichloromethane, dichlorodifluoromethane and dichlorotetrafluoroethane are the most commonly used propellants in aerosol formulations for administration by inhalation.

Chlorofluorocarbons have been implicated in the destruction of the ozone layer and their production is being phased out. Hydrofluorocarbon 134a (HFC-134a, 1,1,1,2-tetrafluoroethane) and hydrofluorocarbon 227 (HFC-227, 1,1,1,2,3,3,3-heptafluoropropane) are viewed as being more ozone friendly than many chlorofluorocarbon propellants; furthermore, they have low toxicity and vapor pressures suitable for use in aerosols.

U.S. Pat. No. 4,352,789 discloses a self-propelling, powder dispensing aerosol composition comprising between about 0.001 and 20 percent by weight of a finely-divided solid material coated with a dry coating of a perfluorinated surface-active dispersing agent of a particular type which constitutes between about 0.1 to 20 percent by weight of the coated solid and a halogenated propellant. The solid material can be a medicament. The use of 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane as a propellant is not specifically disclosed.

SUMMARY OF THE INVENTION

This invention provides suspension aerosol formulations comprising an effective amount of a powdered medicament, between about 0.001 and 0.6 percent by weight of a perfluorinated surface-active dispersing agent and a propellant comprising a hydrofluorocarbon selected from the group consisting of 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoropropane, and a mixture thereof.

The perfluorinated surface-active agent is selected from the group consisting of a perfluorinated sulfonamido alcohol phosphate ester having the general formula

$$[R_fSO_2N(R)R'O]_mP(=O)(OH)_{3-m}$$

wherein R_f is a perfluorinated radical selected from the group consisting of aliphatic C_nF_{2n+1} and cycloaliphatic C_nF_{2n-1} where n is an integer from about 4 to about 10, R is selected from the group consisting of hydrogen and alkyl having about 4 to about 12 carbon atoms, R' is alkylene having about 2 to about 8 carbon atoms and m is an integer from 1 to 3, and a mixture of two or more of said esters;

the formulation exhibiting substantially no growth in particle size or change in crystal morphology of said medicament over a prolonged period, being substantially readily redispersible, and upon redispersion not flocculating so quickly as to prevent reproducible dosing of the medicament. Preferably, the formulation is prepared by combining the dispersing agent and propellant rather than coating the dispersing agent onto the powdered medicament prior to addition of said propellant.

The pharmaceutical suspension aerosol formulations of the invention are suitable, for example, for dermal, pulmonary, or mucosal (e.g., buccal or nasal) administration.

DETAILED DESCRIPTION OF THE INVENTION

The term "suspension aerosol" means that the medicament is in powder form and is substantially insoluble in the propellant.

By "prolonged period" as used herein in the context of crystallization is meant at least about four (4) months.

The medicament is micronized, that is, over 90 percent of the particles have a diameter of less than about 10 microns.

The medicament is generally present in an amount effective to bring about the intended therapeutic effect of the medicament, i.e., an amount such that one or more metered volumes of the formulation contains an effective amount of the drug. The amount of medicament, however, depends on the potency of the particular medicament being formulated. Generally, the medicament constitutes from about 0.01 to 5 percent by weight of the total weight of the formulation, preferably about 0.01 to about 2 percent by weight of the total weight of the formulation.

Medicaments for delivery by inhalation include, for example, analgesics, anginal preparations, antiallergics, antibiotics, antihistamines, antiinflammatories, antitussives, bronchodilators, enzymes, hormones, peptides, steroids, or a combination of these.

Examples of medicaments falling within the above therapeutic classes are: adrenochrome, albuterol, albuterol sulfate, atropine methylnitrate or sulfate, beclomethasone dipropionate, chlorotetracycline, codeine, colchicine, cortisone, disodium cromoglycate, ephedrine, ephedrine hydrochloride or sulfate, epinephrine bitartrate, fentanyl, flunisolide, formoterol, glucagon, heparin, hydrocortisone, hydroxy-tetracycline, insulin, isoproterenol hydrochloride or sulfate, morphine, nedocromide, neomycin, oscapine, penicillin, phenylephrine bitartrate or hydrochloride, phenylpropanolamine hydrochloride, pirbuterol acetate or

hydrochloride, prednisolone, salmeterol, streptomycin, tetracycline, triamcinolone acetonide, and trypsin.

Preferred medicaments in the practice of this invention include albuterol, albuterol sulfate, beclomethasone dipropionate, disodium cromoglycate, epinephrine bitartrate, fenoterol hydrobromide, ipratropium bromide, isoproterenol hydrochloride, isoproterenol sulfate, metaproterenol sulfate, phenylephrine bitartrate, phenylephrine hydrochloride, pirbuterol acetate, pirbuterol hydrochloride, procaterol hydrochloride, salmeterol, triamcinolone acetonide, and mixtures thereof.

Perfluorinated surface-active dispersing agents useful in the invention are perfluorinated sulfonamido alcohol phosphate esters or mixtures of such compounds that are soluble in 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, or a mixture thereof.

Suitable perfluorinated sulfonamido alcohol phosphate esters include those described in U.S. Pat. No. 3,094,547, which is incorporated herein by reference, having the general formula:

$$[R_fSO_2N(R)R'O]_mP(=O)(OH)_{3-m}$$

where R_f is a perfluorinated radical selected from the group consisting of aliphatic C_nF_{2n+1} and cycloaliphatic C_nF_{2n-1}, where n is an integer from about 4 to about 10, R is selected from the group consisting of hydrogen and alkyl having about 4 to about 12 carbon atoms, R' is alkylene having about 2 to about 8 carbon atoms and m is an integer from 1 to 3.

Particularly preferred perfluorinated sulfonamido alcohol phosphate esters include bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate, tris(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate, and mixtures thereof.

For some medicaments a combination of the bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate and the tris(perfluorooctyl-N-ethylsulfonamidoethyl)-phosphate affords aerosol formulations with superior suspension qualities compared to suspensions obtained by using either ester alone. The total amount of ester and the ratio of the bis(perfluorooctyl-N-ethyl-sulfonamidoethyl)phosphate to the tris(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate can be optimized by those skilled in the art for particular medicaments.

The perfluorinated surface-active dispersing agent preferably has a solubility of at least 0.1 percent by weight, more preferably at least 0.3 percent by weight, and most preferably at least 0.8 percent by weight in the propellant.

The perfluorinated surface-active dispersing agent constitutes from about 0.001 to about 0.6 percent by weight, preferably about 0.001 to about 0.5 percent by weight, of the aerosol formulation. The particular preferred amount depends on the particular medicament being formulated and on the particular surface-active dispersing agent being used. It is preferred to use approximately the minimum amount of agent needed to provide a suitable suspension.

The hydrofluorocarbon or mixture thereof is preferably the only propellant present in the formulations of the invention. However, one or more other propellants such as propellant 142b (1-chloro-1,1-difluoroethane) can also be present.

The suspension aerosol formulations of the invention can be prepared by first preparing a solution of the perfluorinated surface-active dispersing agent in the propellant and then suspending the medicament in the solution. In order to prepare a formulation in this manner, the perfluorinated surface-active dispersing agent is placed in an aerosol vial, a continuous valve is crimped onto the vial and the vial is pressure filled with the propellant. The vial is shaken on an automatic shaker until all of the dispersing agent is in solution.

The micronized medicament is then placed in a separate aerosol vial, a continuous valve is crimped onto the vial and the vial is pressure filled with the previously prepared solution. The medicament is then dispersed in the solution by mixing or homogenizing. If the medicament being formulated is moisture sensitive, these steps should be performed in a dehumidified atmosphere using only dry materials and equipment.

The following examples are provided to illustrate the invention but should not be construed as limiting the invention.

In the following examples the quality of the aerosol suspension is rated on a scale of 1 to 5 with 1 indicating a "poor" suspension and 5 indicating an "excellent" suspension. A poor suspension is characterized by one or more of the following: it has a rapid rate of settling or separation, it is difficult to redisperse after settling or separation, it forms large flocs quickly, or it exhibits crystal formation. In contrast, an excellent suspension is slow to settle or separate, is easily redispersed, has minimal flocculation, and exhibits no crystallization or crystal morphology changes. Substantially no crystal formation, relative ease of redispersion, and absence of rapid flocculation after redispersion are important properties in order to provide reproducible dosing of the medicament. Absence of substantial crystal formation provides for maximization of the fraction of the dose deliverable to the target area of the lung. Ease of redispersion permits dosing of a uniform suspension. Finally, rapid flocculation results in a large variation in the dose delivered from the aerosol canister. Suspensions exhibiting a rating of 1 or 2 are not considered desirable in terms of an overall balance of properties of degree of crystallization, ease of redispersibility, and nature of any flocculation, whereas ones exhibiting a rating of 3, 4 or 5 are considered desirable and fall within the scope of this invention.

As used in the Examples below, the term "diester" refers to bis(perfluorooctyl-N-ethyl-sulfonamidoethyl)phosphate, and the term "triester" refers to tris(perfluorooctyl-N-ethylsulfonamidoethyl)-phosphate. Except as otherwise indicated the propellant in the Examples below is 1,1,1,2-tetrafluoroethane (HFC-134a).

Example 1

A 11.528 mg portion of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate was placed in a 4 ounce vial, the vial was sealed with a continuous valve then pressure filled with 115.65 g of 1,1,1,2-tetrafluoroethane. The vial was then shaken on an automatic shaker for 15 minutes. The resulting stock solution contained 0.01 % by weight of bis(perfluorooctyl-N-ethylsulfonamidoethyl)-phosphate. A 100 mg portion of micronized albuterol sulfate was placed in a 15 cc vial along with 5 mL of glass beads, the vial was sealed with a continuous valve then pressure filled with the previously prepared stock solution. The vial was shaken on a WIG-L-BUG™ mixer for 30 seconds. The resulting suspension contained 0.5% by weight of albuterol sulfate and had a quality rating of 5 (excellent).

Examples 2-13

Using the general method of Example 1, a series of micronized albuterol sulfate suspensions were prepared. Table 1 shows the amount (percent by weight based on the total weight of the formulation) and identity of the surface-active dispersing agent (ratios are weight:weight) used and the quality rating of the suspension. The suspensions of Examples 2 and 3 contained 0.5% by weight of albuterol sulfate, that of Example 4 contained 0.46% by weight and the remaining Examples contained 0.45 % by weight of albuterol sulfate.

Table 1

Example	Surface-Active Dispersing Agent		Rating
2	0.005%	diester	3
3	0.05%	diester	5
4	0.3%	diester	3
5	0.005%	3:1 diester:triester	5
6	0.01%	8:1 diester:triester	4
7	0.05%	38:1 diester:triester	3
8	0.005%	4:3 diester:triester	5
9	0.01%	8:3 diester:triester	4
10	0.05%	38:3 diester:triester	3
11	0.005%	4:13 diester:triester	5
12	0.01%	8:13 diester:triester	5
13	0.05%	38:13 diester:triester	3

Examples 14-18

Using the general method of Example 1, a series of suspension aerosol formulations containing 0.5% percent by weight micronized pirbuterol hydrochloride was prepared. Table 2 shows the amount (percent by weight based on the total weight of the formulation) and identity of the surface-active dispersing agent used and the suspension quality rating.

Table 2

Example	Surface-Active Dispersing Agent		Rating
14	0.05%	diester	5
15	0.10%	diester	5
16	0.15%	diester	5
17	0.20%	diester	5
18	0.01%	diester	2

Examples 19-27

Using the general method of Example 1, a series of aerosol suspension formulations containing 1.6% by weight based on the total weight of the formulation of micronized disodium cromoglycate was prepared. Table 3 shows the amount (percent by weight based on the total weight of the formulation) and identity (ratios are weight:weight) of the surface-active dispersing agent used and the suspension quality rating.

Table 3

Example	Surface-Active Dispersing Agent		Rating
19	0.03%	diester	1
20	0.05%	diester	1
21	0.01%	diester	1
22	0.3%	diester	3
23	0.3%	1:1 diester:triester	4
24	0.3%	triester	3
25	0.05%	1:1 diester:triester	3
26	0.1%	1:1 diester:triester	5
27	0.15%	1:1 diester:triester	5

Examples 28-40

Using the general method of Example 1, a series of suspension aerosol formulations containing 0.45% by weight of micronized pirbuterol acetate was prepared. Table 4 shows the amount (percent by weight

based on the total weight of the formulation) and identity (ratios are weight:weight) of the surface-active dispersing agent used and the suspension quality rating.

Table 4

Example	Surface-Active Dispersing Agent		Rating
28	0.3%	diester	1
29	0.01%	diester	3
30	0.05%	diester	2
31	0.10%	diester	2
32	0.15%	diester	2
33	0.20%	diester	2
34	0.005%	3:1 diester:triester	2
35	0.005%	4:3 diester:triester	2
36	0.005%	4:13 diester:triester	2
37	0.1%	3:1 diester:triester	2
38	0.1%	1:1 diester:triester	2
39	0.3%	3:1 diester:triester	2
40	0.5%	3:1 diester:triester	2

Examples 41-46

Using the general method of Example 1, a series of suspension aerosol formulations containing 0.5% by weight based on the total weight of the formulation of micronized epinephrine bitartrate was prepared. Table 5 shows the amount (percent by weight based on the total weight of the formulation) and identity (ratios are weight:weight) of the surface-active dispersing agent used and the suspension quality rating.

Table 5

Example	Surface-Active Dispersing Agent		Rating
41	0.05%	1:1 diester:triester	5
42	0.1%	1:1 diester:triester	2
43	0.15%	1:1 diester:triester	2
44	0.05%	diester	4
45	0.1%	diester	2
46	0.15%	diester	2

Example 47

A 16.6 mg portion of perfluorooctyl-N-ethylsulfonamidoethylphosphate was mixed with 1 g of ethanol in a 4 gram glass vial. The resulting solution was transferred to a 4 ounce glass aerosol vial which was then sealed with a continuous valve and pressure filled with 100 g of 1,1,1,2-tetrafluoroethane to give a stock solution containing 0.016 percent by weight of the ester and 1 percent by weight of ethanol. A 100 mg portion of micronized albuterol sulfate was placed in a 15 cc glass vial along with 5 mL of glass beads, the vial was sealed with a continuous valve and then pressure filled with the stock solution. The vial was placed on a WIG-L-BUG™ mixer for at least 30 seconds. The resulting suspension contained 0.5% by weight of albuterol sulfate and had a quality rating of 2.

Example 48

Using the general method of Example 47, a suspension aerosol containing 0.5% by weight of micronized albuterol sulfate, 0.05% by weight of perfluorooctyl-N-ethylsulfonamidoethylphosphate, 1.2% by weight of ethanol and 1,1,1,2-tetrafluoroethane was prepared. The resulting suspension had a quality rating of 1.

Example 49

Using the general method of Example 47, a suspension aerosol containing 0.5% by weight of micronized albuterol sulfate, 0.005% by weight of perfluorooctyl-N-ethylsulfonamidoethylphosphate, 0.5% by weight of ethanol and 1,1,1,2-tetrafluoroethane was prepared. The resulting suspension had a quality rating of 4.

Example 50

A 10.0 mg portion of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate and a 50.7 mg portion of tris(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate were placed in a vial, the vial was sealed with a continuous valve then pressure filled with 99.879 g of 1,1,1,2-tetrafluoroethane. The resulting stock solution contained 0.01% by weight of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate and 0.05% by weight of tris(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate. A 30 mg portion of micronized beclomethasone dipropionate was placed in a vial along with 3 mL of glass beads, the vial was sealed with a continuous valve and pressure filled with 10 g of the previously prepared stock solution. The vial was placed on a WIG-L-BUG™ mixer for at least 30 seconds. The resulting suspension contained 0.3% by weight of beclomethasone dipropionate and had a quality suspension rating of 4 (excellent).

Examples 51-55

Using the general method of Example 50 and the stock solution prepared in Example 50, a series of suspension aerosols was prepared. Table 6 shows the amount (percent by weight based on the total weight of the formulation) and identity of the medicament used and the quality rating of the suspension. All of the suspensions contained 0.01% by weight of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate and

0.05% by weight of tris(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate.

Table 6

Example	Medicament	Rating
51	0.3% triamcinolone acetonide	5
52	0.5% pirbuterol acetate	5
53	1.5% disodium cromoglycate	5
54	0.5% albuterol sulfate	5
55	0.45% salmeterol	3

Examples 56-58

Using the general method of Example 1, a series of suspension aerosol formulations containing 0.1% by weight of micronized salmeterol was prepared. Table 7 shows the amount (percent by weight based on the total weight of the formulation) and identity of the surface-active dispersing agent used and the suspension quality rating.

Table 7

Example	Surface-Active Dispersing Agent		Rating
56	0.01%	diester	4
57	0.005%	diester	5
58	0.001%	diester	5

Examples 59-64

A series of suspension aerosol formulations in which 1,1,1,2,3,3,3-heptafluoropropane (HFC-227) serves as the propellant was prepared using the general method of Example 1. Table 8 shows the amount (percent by weight based on the total weight of the formulation) and identity of the surface-active dispersing agent used and the suspension quality rating. The formulations of Examples 59-61 contained 0.3 percent by weight based on the total weight of the formulation of

micronized triamcinolone acetonide. Those of Examples 62-64 contained 0.5 percent by weight of micronized pirbuterol acetate.

Table 8

Example	Surface-Active Dispersing Agent		Rating
59	0.025%	diester	4
60	0.05%	1:4 diester:triester	5
61	0.005%	4:1 diester:triester	5
62	0.025%	diester	5
63	0.05%	1:4 diester:triester	4
64	0.005%	4:1 diester:triester	4

In the claims that follow, all weight percentages are based on the total weight of the formulation unless otherwise stated.

WHAT IS CLAIMED IS:

1. A suspension aerosol formulation, comprising: a propellant comprising a hydrofluorocarbon selected from the group consisting of 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3,3-heptafluoropropane, and a mixture thereof; a therapeutically effective amount of a powdered medicament; and between about 0.001 and 0.6 percent by weight of a surface-active dispersing agent of the formula

$$[R_fSO_2N(R)R'O]_mP(=O)(OH)_{3-m}$$

wherein R_f is a perfluorinated radical selected from the group consisting of aliphatic C_nF_{2n+1} and cycloaliphatic C_nF_{2n-1} where n is an integer from about 4 to about 10, R is selected from the group consisting of hydrogen and alkyl having about 4 to about 12 carbon atoms, R' is alkylene having about 2 to about 8 carbon atoms and m is an integer from 1 to 3, and mixture of two or more of said esters;

the formulation exhibiting substantially no growth in particle size or change in crystal morphology of said medicament over a prolonged period, being substantially readily redispersible, and upon redispersion not flocculating so quickly as to prevent reproducible dosing of the medicament.

2. A suspension aerosol formulation according to Claim 1 wherein said powdered medicament is present in an amount of about 0.01 to 2 percent by weight; said formulation being prepared by combining said dispersing agent and propellant rather than coating said dispersing agent onto said powdered medicament prior to addition of said propellant.

3. A suspension aerosol formulation according to Claim 1 wherein said dispersing agent is present in an amount of about 0.001 to 0.5 percent by weight.

4. A suspension aerosol formulation according to Claim 1 wherein said dispersing agent has a solubility of at least 0.3 percent by weight in said propellant.

5. A suspension aerosol formulation according to Claim 4 wherein said dispersing agent has a solubility of at least 0.8 percent by weight in said propellant.

6. A suspension aerosol formulation according to Claim 1 wherein said dispersing agent is selected from the group consisting of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate, tris(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate, and mixtures thereof.

7. A suspension aerosol formulation according to Claim 1 wherein said medicament is selected from the group consisting of an analgesic, an anginal preparation, an antiallergic, an antibiotic, an antihistamine, an antiinflammatory, an antitussive, a bronchodilator, an enzyme, a hormone, a peptide, a steroid, and mixtures thereof.

8. A suspension aerosol formulation according to Claim 1 wherein said medicament is selected from the group consisting of albuterol, albuterol sulfate, beclomethasone dipropionate, disodium cromoglycate, epinephrine bitartrate, fenoterol hydrobromide, ipratropium bromide, isoproterenol hydrochloride, isoproterenol sulfate, metaproterenol sulfate, phenylephrine bitartrate, phenylephrine hydrochloride, pirbuterol acetate, pirbuterol hydrochloride, procaterol

hydrochloride, salmeterol, triamcinolone acetonide, and mixtures thereof.

9. A suspension aerosol formulation according to Claim 1 wherein 1,1,1,2-tetrafluoroethane is essentially the only propellant, and comprising between 0.1 and 1.0 percent by weight of albuterol sulfate having a substantially uniform particle size of less than about 10 microns in diameter, and between about 0.008 and about 0.06 percent by weight of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate.

10. A suspension aerosol formulation according to Claim 1 wherein 1,1,1,2-tetrafluoroethane is essentially the only propellant, and comprising between about 0.5 and about 2 percent by weight of disodium cromoglycate having a substantially uniform particle size of less than about 10 microns in diameter, and between about 0.05 and about 0.4 percent by weight of a mixture of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate and tris(perfluoro-octyl-N-ethylsulfonamidoethyl)phosphate.

11. A suspension aerosol formulation according to Claim 10 wherein said bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate and said tris(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate are present in about equal amounts by weight.

12. A suspension aerosol formulation according to Claim 1 wherein 1,1,1,2-tetrafluoroethane is essentially the only propellant, and comprising between about 0.1 and about 1 percent by weight of epinephrine bitartrate having a substantially uniform particle size of less than about 10 microns in diameter, and between about 0.02 and about 0.07 percent by weight of a mixture of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate and tris(perfluorooctyl-N-ethylsulfonamidoethyl)-phosphate.

13. A suspension aerosol formulation according to Claim 12 wherein said bis(perfluorooctyl-N-ethyl-sulfonamidoethyl)phosphate and said tris(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate are present in about equal amounts by weight.

14. A suspension aerosol formulation according to Claim 1 wherein 1,1,1,2-tetrafluoroethane is essentially the only propellant, and comprising between about 0.1 and about 1 percent by weight of epinephrine bitartrate having a substantially uniform particle size of less than about 10 microns in diameter, and between about 0.02 and about 0.07 percent by weight of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate.

15. A suspension aerosol formulation according to Claim 1 wherein 1,1,1,2-tetrafluoroethane is essentially the only propellant, and comprising between about 0.1 and about 1 percent by weight of pirbuterol hydrochloride having a substantially uniform particle size of less than about 10 microns in diameter, and between about 0.03 and about 0.3 percent by weight of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate.

16. A suspension aerosol formulation according to Claim 1 comprising between about 0.1 and about 1.0 percent by weight of albuterol sulfate having a substantially uniform particle size of less than about 10 microns in diameter, and between about 0.004 and about 0.02 percent by weight of a mixture of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate and tris(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate, with the proviso that the ratio by weight of said bis ester to said tris ester is about 8:1 to about 1:4.

17. A suspension aerosol formulation according to Claim 1, prepared by combining the dispersing agent and the propellant rather than coating the dispersing

agent onto the powdered medicament prior to addition of said propellant.

18. A suspension aerosol formulation according to Claim 1 comprising 1,1,1,2-tetrafluoroethane as essentially the only propellant.

19. A suspension aerosol formulation according to Claim 1 comprising 1,1,1,2,3,3,3-heptafluoropropane as essentially the only propellant.

20. A suspension aerosol formulation according to Claim 1 wherein 1,1,1,2-tetrafluoroethane is essentially the only propellant, and comprising: about 0.02 to about 0.07 percent by weight of a mixture of about one part by weight bis(perfluorooctyl-N-ethyl sulfonamidoethyl)phosphate and about five parts by weight tris(perfluorooctyl-N-ethylsulfonamidoethyl)-phosphate; and a medicament having substantially uniform particle size of less than about 10 microns in diameter selected from the group consisting of beclomethasone dipropionate in an amount of about 0.1 to about 0.5 percent by weight, triamcinolone acetonide in an amount of about 0.1 to about 0.5 percent by weight, pirbuterol acetate in an amount of about 0.3 to about 0.7 percent by weight, disodium chromoglycate in an amount of about 1.0 to about 2.0 percent by weight, albuterol sulfate in an amount of about 0.3 to about 0.7 percent by weight, and salmeterol in an amount of about 0.4 to about 0.5 percent by weight.

21. A suspension aerosol formulation according to Claim 1 wherein 1,1,1,2-tetrafluoroethane is essentially the only propellant, and comprising about 0.05 to about 0.2 percent by weight of salmeterol having a substantially uniform particle size of less than about 10 microns in diameter and about 0.001 to about 0.01 percent by weight bis(perfluorooctyl-N-ethylsulfonamido-ethyl)phosphate.

22. A suspension aerosol formulation according to Claim 1 wherein 1,1,1,2,3,3,3-heptafluoropropane is essentially the only propellant and comprising about 0.1 to about 0.5 percent by weight triamcinolone acetonide having a substantially uniform particle size of less than about 10 microns in diameter and about 0.005 to about 0.05 percent by weight of a dispersing agent selected from the group consisting of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate and a mixture of bis(perfluorooctyl-N-ethyl-sulfonamidoethyl)phosphate and tris(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate.

23. A suspension aerosol formulation according to Claim 1 wherein 1,1,1,2,3,3,3-heptafluoropropane is essentially the only propellant and comprising about 0.3 to about 0.7 percent by weight pirbuterol acetate having a substantially uniform particle size of less than about 10 microns in diameter and about 0.005 to about 0.05 percent by weight of a dispersing agent selected from the group consisting of bis(perfluorooctyl-N-ethyl-sulfonamidoethyl)phosphate and a mixture of bis(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate and tris(perfluorooctyl-N-ethylsulfonamidoethyl)phosphate.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/04423

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/12 A 61 K 9/72

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	US,A,4352789 (C.G. THIEL) 5 October 1982, see claims 1-7,11-18 (cited in the application) ---	1,2,6-8 ,17-19
A	US,A,3094547 (R.F. HEINE) 18 June 1963, see claims 1,3,5,7; column 3, lines 16-18; column 4, lines 53-54 (cited in the application) ---	1,6
A	STN International Information Services Data Base: Chemical Abstracts, Accession No.: 89(14):117545k, & JP-A-53 031 582 (DAIKIN KOGYO CO., LTD) 24 March 1978, see abstract -----	1,18-19

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
06-09-1991	17. 10. 91
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Mme. M. van der Drift

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9104423 SA 48957

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 25/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4352789	05-10-82	None	
US-A- 3094547		CH-A- 421083 DE-A,B,C 1493944 FR-A- 1317427 GB-A- 1002680	08-06-72